INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Advances In Skin Lightening Agents: Mechanisms, Efficacy, And Safety Considerations

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ARTICLE INFO

Received: 01 June 2024
Accepted: 05 June 2024
Published: 18 June 2024

Keywords:
Skin lightening, Hyperpigmentation, Natural Bioactive components, Tyrosinase inhibitors

DOI:
10.5281/zenodo.12105303

ABSTRACT

Skin whitening has become a global beauty trend driven by cultural, social and personal preferences for beautiful skin. Over the years, extensive research has been done to develop effective and safe skin care products. Doctors and dermatologists often look for long-term cosmetic products, including formulations and topical products, to control hyperpigmentation. A particular concern expressed by many women is the desire to show beautiful skin, reduce yellow or pale tones, and reduce the symptoms of hyperpigmented spots such as age spots or sunspots. While kojic acid, hydroquinone, and corticosteroids being conventional depigmenting agents have been shown to be effective, their long-term use may pose serious safety concerns, including aging, atrophy, carcinogenicity, and other local side effects or disease. However, exploring the benefits of natural and herbal products offers promising opportunities to create new products designed to address pigmentation issues while reducing safety risks.

INTRODUCTION

The skin is the largest organ of the human body with three main tissues: epidermis, dermis and subcutaneous, for the purpose of safeguarding and vibrant vitality1. Epidermis contains melanocytes that produce melanin, responsible for skin aging and protection from UV radiation. The interface between the dermis and epidermis, called the dermal-epidermal junction, acts as a barrier preventing the penetration of macromolecules and cells. Melanin is an important pigment in determining human skin color2, excessive production of melanin causes hyperpigmentation of skin. Currently pharmaceutical and Cosmetic companies are on the verge of discovering and developing drugs that can reduce

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

hyperpigmentation by blocking the production of melanin 3,4. Melanogenesis, the process of melanin production, transpires within specialized cells called melanocytes. These melanocytes establish physical and functional interrelationships with neighboring skin cell types, fostering autocrine and paracrine interactions essential for the regulation and coordination of melanin synthesis. Autocrine signaling allows melanocytes to produce and release chemical signals that act on their own cell surface receptors, regulating their own activity and melanin production. Paracrine signaling involves the secretion of chemical signals by melanocytes that act on nearby cells, influencing the behavior and functions of surrounding keratinocytes, fibroblasts, and other skin cell types. This autocrine and paracrine interplay between melanocytes and other skin cells ensures the coordination of melanin production, distribution, and response to environmental and physiological cues. Melanin synthesis also occurs through various oxidation reactions involving the enzyme tyrosinase, which catalyzes the hydroxylation of tyrosine to L-DOPA, oxidation of L-DOPA to dopaquinone and Oxidation of L-tyrosine to dopaquinone (DQ) 5. Dopaquinone acts as a precursor for the synthesis of eumelanin and pheomelanin 6,7. The formation of DQ is a critical step in melanin production, as the subsequent reaction occurs spontaneously under physiological pH conditions. Dopachrome is gradually broken down, resulting in the formation of dihydroxy indole (DHI) and dihydroxyindole-2-carboxylic acid (DHICA). Finally, these dihydroxy indoles (DHI and DHICA) are oxidized to eumelanin. Subsequent oxidation of this compound results in the production of benzothiazine and finally pheomelanin. Tyrosinase is an enzyme that acts as a catalyst and a vital protein in melanin synthesis, that defines our skin color. It carefully manages the conversion of the tyrosine an amino acid into melanin precursors, ensuring precise control over melanin production. Tyrosinase inhibitors exert their effect by targeting tyrosinase activity inhibition which hinders melanin synthesis, consequently leading to a reduction in skin pigmentation resulting in lighter skin8,9.These inhibitors interfere with key steps within the melanin synthesis pathway such as the transformation of tyrosine to dopaquinone and formation of melanin precursors 10,11. Sunspots and freckles often result from prolonged sun exposure and are associated with localized melanin overproduction. Thus, tyrosinase inhibitors, particularly those with sunscreen properties, can prevent the formation of sunspots and freckles by reducing the enzymatic activity of tyrosinase and minimizing melanin synthesis 12. Regular use of such inhibitors helps in sun protection regimen and maintain a more uniform skin complexion. For instance, combining tyrosinase inhibitors with exfoliating agents like alpha-hydroxy acids or retinoids can enhance the removal of existing pigmented cells and inhibit new melanin synthesis 13. Additionally, the use of antioxidants alongside tyrosinase inhibitors can provide synergistic effects by neutralizing free radicals and minimizing oxidative stress, which can contribute to skin darkening. Skin pigmentation and skin lightening includes various treatments which include chemical peels, microdermabrasion, LED therapy, and microcurrents. Chemical peels promote healthier skin, while Spectra Carbon Peel reduces pigmentation while promoting even tone. Anti-Clock facials are suitable for dry, sagging, and dehydrated skin, but may cause temporary redness or sensitivity. Glutathione skin whitening is popular for lightening darker skin tones but can cause rashes, allergies, dizziness, and vomiting. Hydroquinone is an effective depigmenting agent, but side effects like dermatitis, dryness, redness, swelling, and skin irritation can occur. Light-

emitting diode (LED) therapy uses specific wavelengths of light to address hyperpigmentation. However, none of these treatments are satisfactory in terms of efficacy and long-term results14,15. Depigmenting substances should be precise in targeting overactive melanocytes without unwanted short- or long-term effects. Natural skin lightening approaches, such as plant extracts and bioactives, are worth exploring.With more depigmentation options available, the number of compounds with depigmentation activity has increased.Henceforth it is felt worthwhile to have a deep exploration of different alternate, traditional approaches against skin lightening. Recent research investigations are mainly focused on inhibition of tyrosinase activity by natural phytoconstituents, towards melanin synthesis, leading to reduction in skin pigmentation16,17.

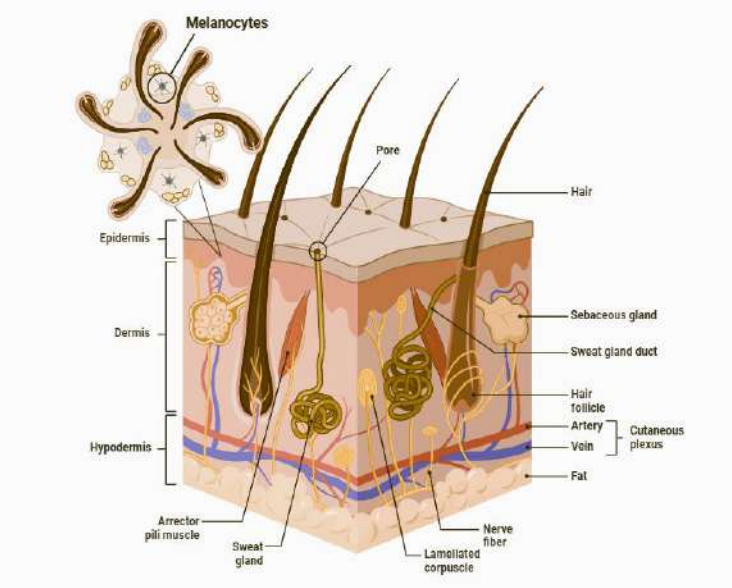

Fig.1: Morphology of skin1,2,5

METHODOLOGY:

This review is based on a thorough examination of various publications, especially those focusing on using plant extracts and natural components for cosmetics. A comprehensive search across four major databases: ScienceDirect, PubMed, Google Scholar, and Scopus were conducted. To find relevant information, specific keywords such as "skin lightening," "isolated compounds," "tyrosinase inhibitors," "natural plants and their components," and "Anti melanogenic activity" were carefully selected and explored. This approach allowed in gathering a broad range of research insights, enabling us to provide an insightful analysis of plant-based cosmetic ingredients and their potential benefits.

BIOACTIVES IN NATURAL SKIN LIGHTENING:

Plant extracts have shown significant inhibitory effects on melanin formation, proving to be more potent and better than hydroquinone, arbutin and kojic acid. Unlike these traditional depigmenting agents, plant extracts do not exhibit cytotoxic or mutagenic properties towards melanocytes. The abundance of natural resources provides a wide variety of extracts and isolated compounds, indicating the vast untapped potential of these natural extracts in the field of skin lightening. However, further research and exploration are necessary to comprehend and harness the effectiveness of plant extracts for the development of safer and more efficient skin-lightening

solutions. Bioactives there of exhibiting anti-melanogenic activity are as follows

Artocarpus plants and its chemical components

Artocarpus plants have been scrutinized for their remarkable potential in the dermatological applications, particularly concerning the development of agents targeting skin pigmentation Through meticulous In vitro experimentation, various compounds were derived from Artocarpus plants18,19. Table I represents Compounds from Artocarpus Plants with Inhibitory Effects on Melanin Production and Tyrosinase Activity28

Table I : Summarizes and highlights the main compounds derived from Artocarpus plants that exhibit inhibitory effects on melanin production and tyrosinase activity.

Compound	Source	Mechanism and Effects
Andalasin	Artocarpus rigidus	Inhibition of tyrosinase enzyme, Skin lightening [18,19]
Artocarbene	Artocarpus incisus and others	Inhibition of tyrosinase enzyme, potential for skin brightening and hyperpigmentation management[27]
Artocarpanone	Artocarpus elasticus bark	Melanin inhibition providing more even skin tone[20]
Artocarpesin	Various Artocarpus plants	Tyrosinase enzymatic action inhibition, potential for skin whitening and addressing hyperpigmentation[21]
Artogomezianol	Artocarpus gomezianus heartwood	Inhibition of tyrosinase activity, treatment of hyperpigmentation[24]
Chlorophorin	Artocarpus heterophyllus sapwood	Inhibitory activity against tyrosinase, treatment of hyperpigmentation[23,24]
Extracts from A. incisus	Artocarpus incisus	Potential skin lightening agent, treatment for pigmentation problems[25,27]
Norartocarpetin	Various sources Artocarpus plants	Downregulation of phospho-cAMP response, potential for modulating melanin production and skin pigmentation[26,27]

Morus australis and its chemical components:

The extract of Morus australis has shown to have potential to be a rich source of tyrosinase inhibitors. These inhibitors are suitable for many applications, including anti-inflammatory agents and skin lightening agents in cosmetics. Sanggenon type prenyl flavanones, and its derivatives (sanggenon O, sanggenon C, sanggenon M), chalcomoracin, sorocein H and kuwanon J obtained from Morus australis were investigated as tyrosinase inhibitors. More importantly, sanggenon D exhibited stronger inhibitory activity compared to kojic acid and arbutin. Also, in the tyrosinase inhibition test, compounds such as oxidized resveratrol, sanggenon T and sanggenon O proved to be more potent against tyrosinase than the still known tyrosinase inhibitor. This data supports the utility of Morus australis root extract as a potential source for the development of tyrosinase inhibitors. 28,29

Scutellaria baicalensis and its chemical components:

Baicalein, an important flavonoid found in Scutellaria baicalensis, is considered a potent tyrosinase inhibitor, an important enzyme involved in melanin production. The mechanism by which baicalein inhibits tyrosinase was investigated through a combination of enzyme kinetics, spectroscopic methods, and computational simulations. 30,31,32 The results showed that baicalein had a significant effect on the diphenolase activity of tyrosinase with an IC50 value of 0.11 µM. Inhibition kinetics showed that baicalein was a complex inhibitor of binding with a Ki value of 0.17µM and 0.56. Also, spectroscopic analysis revealed the formation of a complex between baicalein and tyrosinase, as

evidenced by ultraviolet absorption spectroscopy. Baicalein's ability to control melanin production and potent tyrosinase inhibition make best candidate for skin lightening and hyperpigmentation control.32,33

Rhus succedanea and its chemical components:

The alkyl hydroquinones 10'(Z)-heptadecenylhydroquinones , extracted from the sap of the lacquer tree Rhus succedanea, has emerged as a captivating compound with remarkable potential in inhibiting activity of tyrosinase and production of melanin in animal cells. 34In a clear study by Chen et al., the inhibitory effect of alkylhydroquinone 10'(Z)-heptadecenylhydroquinone on tyrosinase and its superior potency compared to the well-established tyrosinase inhibitor, hydroquinone were unraveled35. The elucidation of alkyl hydroquinone 10'(Z)-heptadecenylhydroquinone's potent impact on tyrosinase activity helps in utilization in preserving the quality of this botanical component susceptible for skin whitening.

Agaricus hondensis mushrooms and its chemical components:

Hydroquinone (HQ) is the primary toxic compound found in Agaricus hondensis mushrooms. This well-studied substance has gained significant recognition as a whitening agent and has been widely employed in cosmetic treatments for hyperpigmentation. In clinical settings, hydroquinone cream is commonly utilized as the standard depigmentation agent. Its therapeutic applications extend to addressing various dyschromia conditions, including melasma, freckles, and post-inflammatory hyperpigmentation. The depigmentation action of hydroquinone stems inhibits melanin synthesis by impeding the conversion of L-3,4-dihydroxyphenylalanine (L-DOPA) into melanin by directly affecting the enzymatic activity of tyrosinase . While hydroquinone remains a commonly prescribed ingredient for skin-lightening purposes, it is essential to acknowledge its potential adverse effects. Skin irritation and burning sensations are among the reported drawbacks associated with its usage. Additionally, hydroquinone has been identified as mutagenic to mammalian cells and exhibits cytotoxicity toward melanocytes 36,37.

Mulberry tree (Morus alba Linn.) and its chemical components:

The Mulberry tree (Morus alba Linn.) a part of the Moraceae family, has been found to possess remarkable tyrosinase inhibition activity, as demonstrated by a recent study. Research focused on investigating the active components present in the extricate obtained from Morus alba Linn twigs. In the evaluation of tyrosinase inhibitory properties were examined, the compound steppogenin exhibited considerable activity with an IC50 value of 0.98 ± 0.01 µM. Notably, the inhibitory effects of steppogenin surpassed those of the positive control kojic acid, a tyrosinase inhibitor. Later, the active components responsible for this inhibition were investigated.38 Among the tested compounds, sanggenon T, oxyresveratrol, kuwanon O and moracenin D exhibited strong activity of tyrosinase inhibition compared to kojic acid, a tyrosinase inhibitor. Notably, a flavone called morusone showed tyrosinase inhibition activity with an IC50 value of 290.00 ± 7.90. These suggest that the extract obtained from the twigs of Morus alba Linn. holds great potential as a natural source of tyrosinase inhibitors and the application of Morus alba twig extract as Anti browning agents can be expected.39

Mung bean (Vigna radiata) and its chemical components:

Mung bean (Vigna radiata) holds significant cultural value worldwide, particularly in Asian countries, where it is widely consumed as a dietary staple and is used in various culinary applications, including soups, stews, salads, desserts, and more.

They are highly nutritious and provide an important source of protein, fiber, and essential nutrients. Beyond its dietary importance, mung bean has a rich history of traditional medicinal usage. In a recent study, a 70% ethanol extract of mung bean was further fractionated using solvents Dichloromethane (CH2Cl2), Ethyl Acetate (EtOAc), and n-Butanol (n-BuOH) to produce four different fractions which included CH2Cl2-soluble in ethyl acetate being soluble, soluble in n-butanol and residual extract fractions. More importantly, the ethyl acetate-soluble fraction exhibits the highest activity against tyrosinase enzyme involved in synthesis of melanin.40 Two pure flavonoids, vitexin and iso-vitexin, were isolated from the EtOAc soluble fraction by enzyme assay-guided fractionation method. These compounds have potent tyrosinase inhibitory activity with IC50 values between 6.3 and 5.6 μg mL-1. This investigation represents the first exploration of the active components present in mung bean targeting mushroom tyrosinase. This highlights the potential of vitexin and iso-vitexin as effective inhibitors of tyrosinase activity.41,42,43

Cudrania cochinchinensis and its chemical components:

The Phytochemical components of each part of Cudrania cochinchinensis, was examined using High-Performance Liquid Chromatography Analysis (HPLC). Remarkably, the stem extract of C. cochinchinensis exhibited the presence of unknown products as tyrosinase inhibitors. Motivated by these findings, further investigations were conducted to identify the chemical constituents in the stem extract, obtained using 95% ethanol.44 The results unveiled the activity of tyrosinase inhibition of specific compounds present in the C. cochinchinensis stem extract. Notably, (±)2,3-cis-dihydromorin, oxyresveratrol and 2,3-trans-dihydromorin, exhibited superior potency as tyrosinase inhibitors, with IC50 values of 31.1 μM, 21.1 μM, and 2.33 μM, respectively. This observation underscores the remarkable potential of Cudrania cochinchinensis stem as a source for effective and potent natural tyrosinase inhibitors. The identified compounds, hold promise for further exploration and application in the development of skincare products and treatments targeting hyperpigmentation disorders.45,46

Licorice root (Glycyrrhiza glabra) and its chemical components:

Licorice root (Glycyrrhiza glabra) possesses medicinal properties attributed to the presence of glabridin, an iso-flavonoid compound. Glabridin exhibits anti-inflammatory and antiplatelet effects by inhibiting cyclooxygenase activity.45 Notably, glabridin has been found to reversibly inhibit tyrosinase, an enzyme involved in melanin synthesis, In the non-competitive situation with the IC50 value is 0.43 μM L-1. The main feature of this interaction is static quenching, in which glabridin effectively quenches the intrinsic fluorescence of tyrosinase. Interestingly, molecular docking studies show that glabridin does not directly act on the active site of tyrosinase. In addition, licorice extract's inhibitory effect on tyrosinase activity was greater than that of glabridin alone. This has led to the search for other substances that contribute to the extract's inhibitory activity. Studies have shown that Isoliquiritigenin found in extract of licorice can inhibit the activity of monophenolase and bisphenolase tyrosinase. In addition, inhibition of tyrosinase activity by Iso liquiritigenin is dose-dependent and correlates with their ability to inhibit production of melanin in melanocytes.47

Apios americana (A. americana) and its chemical components:

Apios americana (A. americana) is a plant from the Fabaceae family, and is indigenous to eastern North America. In a study, A. americana dried tubers were extracted using methanol at room

temperature. The final methanolic extract is concentrated and fractionated using stepwise solvent extraction to obtain the n-hexane, butanol, ethyl acetate and water fractions. From these fractions, the ethyl acetate fraction was further purified using silica gel, Sephadex LH-20 and C-18 column chromatography, and compounds were isolated.48 The structures of these compounds were determined by comparing previous information as well as their spectroscopic data, including circular dichroism (CD), Nuclear Magnetic Resonance Spectra (NMR spectra) and Electrospray Ionization Mass Spectrometry48. Compounds found in the extract such as aromadendrin 5-methyl ether and lupinalbin A, among others were investigated thoroughly. Competitive inhibitors such as 2-hydroxygenistein-7-O-gentibioside and lupinalbin A exhibited a potential Ki value of 10.3 ± 0.8 µM using the Dixon plot. This correlates with its ability of tyrosinase inhibition and potent skin whitening agent. 52

Humulus japonicus and its chemical components:

In the search for natural ingredients with potential cosmetic use, Humulus japonicus was explored. The ethyl acetate soluble fraction of Humulus japonicus exhibited inhibition of tyrosinase activity. Japonicus by High-Performance Liquid Chromatography Mass spectroscopy (HPLC-MS/MS) combined with the tyrosinase assay revealed the presence of phytoconstituents. Results from the HPLC-MS/MS tyrosinase assay were consistent with the tyrosinase-inhibitory activity of the isolated compounds analyzed. N-coumaroyl tyramine and cis-N-coumaroyl tyramine were the main compounds and showed activity of inhibition and as an active ingredient in cosmetics49. In addition, the cosmetic activity of trans-N-coumaroyl tyramine derivatives was investigated using the coating method. Derivatives were first evaluated for Anti tyrosinase activity and then cytotoxicity was evaluated by assays based on mitochondrial activity. The most potent derivatives were then tested in-vitro to inhibit melanogenic activity in two-dimensional monolayers of human melanocytes containing melanocytes and keratinocytes to evaluate their depigmentation activities. Molecular docking shows the interaction between derivatives and tyrosinase and shows their anti-melanogenic activities by inhibiting tyrosinase.50

Allium cepa, and its chemical components:

Quercetin, a flavonoid compound, was discovered in a variety of foods, particularly in fruits, vegetables, and some beverages. has been found to enhance production of melanin per cell in cultured murine B16-F10 melanoma cells. However, this effect can be due to Melano cytotoxicity . At a concentration of 20 µM, quercetin resulted in a 50% loss of viable cells, and nearly complete cell death was observed at 80 µM.53 In the pursuit of discovering new whitening agents, the focus turned to Allium cepa, commonly known as red onion. A compound called quercetin 4'-O-β-D-glucopyranoside was extracted from dried onion peel by bio guided fractionation using mushroom tyrosinase. When using L-tyrosine or L-DOPA as substrate, Quercetin 4'-O-β-D-glucopyranoside exhibits inhibitory activity of tyrosinase enzyme with IC50 values of 4.3 and 52.7 µM, respectively.53 These data indicates that the dried skin of red onion contains ingredients with the potential to be used in skin-whitening cosmetics due to their anti-tyrosinase activity.

Koji bean seeds and its chemical components:

Two metabolites, 7,8,4'-trihydroxyisoflavone and 5,7,8,4'-tetrahydroxyisoflavone, were extracted from koji bean seeds. These compounds have been shown to have a significant effect on the monophenolase and bisphenolase tyrosinase activity. Among these metabolites, 7,3′,4′-trihydroxyisoflavone (7,3′,4′-THIF) drew particular attention.56 Recent studies have shown

that 7,3',4'-THIF causes hypopigmentation effects in B16F10 cells. It was discovered that 7,3′,4′-THIF, in contrast to daidzein, directly and effectively inhibited α-melanocyte-stimulating hormone (MSH)-induced melanin production, both intracellularly and extracellularly, in B16F10 cells. This intriguing effect was attributed to the compound's interaction with the melanocortin 1 receptor (MC1R). Furthermore, the compound modulated the activity of various signaling molecules, including protien kinase B (PKB), p38 Mitogen-Activated Protein Kinase (p38MAPK), and cAMP-dependent protein kinase A(PKA), further influencing the melanin production pathway. 53 Mechanistic investigations, including cAMP and pull-down assays, unveiled that 7,3′,4′-THIF significantly curtailed intracellular cAMP production. Additionally, the compound exhibited a direct binding affinity for MC1R, competing with α-MSH for receptor occupancy. Strikingly, 7,3′,4′-THIF exerted its inhibitory activity not only in B16F10 cells but also in human epidermal melanocytes (HEMs), highlighting its potential agent for regulating melanin production. Collectively, these findings show modes of action of 7,3′,4′-THIF, which specifically targets MC1R and curtails melanin production 54,55.

Phellinus linteus and its chemical components:

Phellinus linteus, a medicinal mushroom, has emerged as a source of natural tyrosinase inhibitors. Among its compounds, protocatechualdehyde, a benzaldehyde type compound, has displayed remarkable tyrosinase inhibitory activity, surpassing that of kojic acid by 7.8-fold. This potent inhibitor holds promise for applications in the field of cosmeceuticals and skincare 57. Furthermore, the complex culture broth of Phellinus linteus has demonstrated significant effects on melanin synthesis and tyrosinase activity. When administered as a drug, culture medium 3-isobutyl-1-methylxanthine (IBMX) reduced proteins related to melanogenesis, including microphthalmia and tyrosinase in cells. Interestingly, this medium does not affect tyrosinase-associated protein 1 and tyrosinase-related protein 2, indicating a selective inhibitory effect on specific components of the melanogenesis pathway. In the exploration of Phellinus linteus the chemical components were isolated from the fruit body. Importantly, compounds such as protocatechualdehyde, 5-hydroxymethyl-2-furaldehyde (HMF) exhibited inhibitory effects on L-tyrosine oxidation catalyzed by mushroom tyrosinase, with IC50 values of 0.40 and 90.8 µg mL-1 weight. 57,58 These findings point to the potential of Phellinus and its derivatives to be important natural tyrosinase inhibitors.

Aloe vera and its chemical components:

Aloe species are known to possess anti-tyrosinase properties, making them potential candidates for managing hyperpigmentation and serving as skin lightening agents. Aloe vera leaf extricate, as well as its bioactive component aloin, were investigated on tyrosinase inhibition activity and was found to be a mixed competitive tyrosinase inhibitor59,60. The researchers conducted a screening of exudates of South African Aloe species to identify those anti-tyrosinase activity. Qualitative screening revealed that 29 Aloe species exhibited inhibitory activity against tyrosinase, Further analysis was conducted through molecular docking, comparing the activity of plicataloside and aloesin. The results indicated that plicataloside exhibited considerably lower docking scores than aloesin ($P < 0.01$), suggesting a stronger inhibitory effect with a lower IC50 value. The findings suggest that certain Aloe species may hold promise for managing hyperpigmentation and acts as skin lightening agents. Aloin has been shown to induce melanin aggregation through the stimulation of alpha-adrenergic receptors, resulting in skin lightening effects. Aloe vera and its constituents as

effective agents for regulating tyrosinase activity and addressing skin pigmentation concerns.60

Carthamus tinctorius L and its chemical components:

Hydroxysafflor yellow A (HSYA) is an active compound derived from Carthami Flos, the flower of safflower (Carthamus tinctorius L.) L in the name refers to the botanist Carl Linnaeus. It is a water-soluble pigment with significant pharmacological properties, making it a subject of extensive research since its isolation in 1993.61 Studies have demonstrated the potential of HSYA in topical applications for mitigating Ultra-violent induced (UV) skin damage. Its antioxidative activity promotes skin recovery, reduces epidermal hyperproliferation, and keeps up the basic integrity of the skin. Additionally, HSYA exhibits strong inhibitory effects on tyrosinase, an enzyme involved in melanin synthesis. It achieves this by binding it to tyrosinase and inducing conformational changes in its tertiary structure. Furthermore, HSYA has shown favorable therapeutic effects in animal models, indicating as protective agent against UV-induced skin damage. Additionally, its potent inhibition of tyrosinase activity positions HSYA as a potential ingredient in the development of skin-whitening products.62,63

Thymus quinquecostatus and its chemical components:

Two varieties of Thymus quinquecostatus are found in Korea: bak-ri-hyang (T. quinquecostatus Celakovsky), which is distributed throughout the Korean Peninsula, and island thyme. The main component identified in the essential oils of both varieties was thymol, with bak-ri-hyang containing 39.8% and island thyme containing 54.7% thymol. Studies have highlighted the potential whitening activity of thymol and its inhibitory effect on tyrosinase, a key enzyme involved in melanin production.66 Further on exploration complex containing thymol ester (3,4,5-methoxycinnamate thymol ester), on melanogenesis in melanin-α and α-melanocyte stimulating hormone inhibitory effect in stimulated B16 cells was reported. It is important to note that while thymol exhibits promising activities, it also demonstrates moderate cytotoxicity towards B16-F10 melanoma cells, with an IC50 value of 400 μM (60.09 μg mL-1). However, this toxic effect can be mitigated by the addition of vitamin D and vitamin C, resulting in increased cell viability by 20% and 40%, respectively. Moreover, the toxic effect of thymol on melanoma cells can be reversed by the treatment of l-cysteine. Thymol, an aromatic monoterpene, exhibits the potential for whitening activity and is considered an important functional compound.67

Morus lhou Koidz., and its chemical components:

The stem barks of Morus lhou Koidz., a cultivated plant with edible properties, have revealed discovery of tyrosinase inhibition. Within this botanical treasure, five distinctive flavones have emerged, showcasing remarkable potential in suppressing the enzymatic activity of tyrosinase.68,69 These compounds have been identified as mormin , kuwanon C, cyclomorusin, morusin and norartocarpetin, adding to the rich phytochemical diversity. To unravel the inhibitory potential of these flavonoids against the monophenolase activity of mushroom tyrosinase, rigorous experimentation was undertaken.64,65 The ensuing revelations divulged the IC50 values for compounds 1-5: a mere 0.088 mM, 0.135 mM, 0.092 mM, 0.250 mM, and 1.2μM, were recorded. Such potency underscores their impact on the catalytic activity of tyrosinase. Norartocarpetin unveils an inhibitory behavior as a time-dependent inhibition against the oxidation of L-tyrosine. Operating under the enzyme isomerization model, this compound exhibits its effect by an apparent inhibition constant of 1.354μM this botanical

revelation from Morus lhou imparts a vivid glimpse into the intricate world of flavones as potent inhibitors of tyrosinase. 66,67

Lippia origanoides,(Aerial parts) Essential Oil

The inhibitory potential of the Essential oils obtained from Lippia origanoides against tyrosinase activity was assessed using L-tyrosine and L-DOPA as substrates was explored. Essential oils, namely Lippia origanoides-1(LiOr-1), LiOr-2, and LiOr-3, were investigated for their ability to inhibit tyrosinase activity, a key enzyme involved in melanin production. These essential oils displayed effective inhibition, particularly in the initial oxidation step, suggesting their potential for skin whitening and managing hyperpigmentation. Additionally, they interacted with copper ions and engaged in hydrogen bonding interactions, controlling inhibitory mechanisms. The essential oils were rich in specific compounds, such as 1,8-cineole, thymol, and (E)-nerolidol, which contributed to their tyrosinase-inhibiting properties. It highlights the promising cosmetic applications of these essential oils in skincare products aimed at addressing skin pigmentation concerns and promoting a more even skin tone.74

Kojic acid

Kojic acid and β-arbutin are widely recognized for their ability to inhibit tyrosinase activity and deoxy arbutin effectively suppressed mushroom tyrosinase (MTYR) activity and reduced melanin content.73 Conversely, α-arbutin and β-arbutin dose-dependently inhibited B16F10 cells melanin content, tyrosinase (BTYR) activity, resulting in decreased melanin content.75,76 Based on these results, kojic acid is the most suitable positive control among the investigated It effectively inhibits both monophenolase and diphenolase activities of mushroom tyrosinase (MTYR), leading to reduced intracellular melanin content without compromising cell viability. 77,78

Andrographis paniculata

Andrographis paniculata, a medicinal plant, has numerous therapeutic properties, including antifungal, antimicrobial, antiprotozoal, antidiabetic, hepatoprotective, insecticidal, and toxicological attributes.79,80,81,82 However, there is a lack of information regarding its potential anti-melanogenic activity.83 A recent study was conducted to explore the anti-melanogenic properties of A. paniculata leaf extract, focusing on its ability to inhibit melanin synthesis, a process relevant to conditions like hyperpigmentation. The study used advanced technology, such as the In-vitro tyrosinase assay and the Mushroom TYR inhibition assay, to quantitatively assess the extract's ability to modulate tyrosinase activity.84,85,86 This assay provides insights into its potential as an anti-melanogenic agent and serves as a reliable model for studying melanin synthesis inhibition.87,88,89,90 The results provide valuable insights for further exploring the potential application of Andrographis paniculata in dermatology and developing novel therapeutic interventions for hyperpigmentation and related skin conditions.91 Below Table II represents the plants and Plant extracts which have shown significant inhibitory effects on melanin formation

Table II : Provided table presents a summary of several plant species and their potential as sources of natural compounds with tyrosinase inhibitory activity. Tyrosinase is an enzyme responsible for melanin synthesis, and its inhibition can play a role in skin lightening and depigmentation.97,98,99

Plant species & Plant part	Location	Chemical Constituents	Mechanism of action and Effects
Agaricus hondensis mushrooms	North America	Hydroquinone	Directly inhibits tyrosinase activity, commonly used in

			depigmentation treatments. [36,37]
Allium cepa	South-west of Asia.	Quercetin 4'-O-β-D-glucopyranoside	Inhibition of tyrosinase enzyme[53]
Aloe vera	Africa, Asia, Europe and America	Aloin	Inducing melanin aggregation via alpha-adrenergic receptors, Regulating tyrosinase activity [59,60]
Andrographis paniculata	Southeastern Asia	Leaf extract	Inhibits melanin synthesis and has potential anti-melanogenic activity.[91,79,80]
Apios americana Dried tubers of A. americana	Southern canada	Lupinalbin A	Competitive inhibition tyrosinase activity with a Ki value of 10.3 ± 0.8 μM [52,52]
Artocarpus heterophyllus	Tropical regions	Dihydromorin, artocarpanone, norartocarpetin, steppogenin, artocarpin, cycloartocarpin, and more	Efficacy in curbing the enzymatic activity of tyrosinase, Anti browning agent.[26,27,22,23,24]
Carthamus tinctorius L	China and Japan	Hydroxysafflor Yellow A	Binds to tyrosinase and induces conformational changes in its tertiary structure, exhibiting strong inhibitory effects on tyrosinase activity. [62,63]
Cudrania cochinchinensis Stem extract	China, Japan, Korea	(±)2,3-cis-dihydromorin, 2,3-trans-dihydromorin, oxyresveratrol	Inhibition of tyrosinase enzyme activity , with IC_{50} of 31.1 μM, 21.1 μM, and 2.33 μM.[45,46]
Danshen-Honghua	N/A	Phenylalanine, 6-Hydroxykaempferol-3,6,7-O-β-D-glucoside, Salvianolic Acid A 6-Hydroxykaempferol-3,6,7-O-β-D-glucoside	Identified in Danshen-Honghua extracts, potential tyrosinase inhibitor. [92]
Gallic acid	N/A	Flavonoid compound	Inhibits melanin synthesis and downregulates melanogenesis-related proteins [93,94,95]
Glycyrrhiza glabra Licorice root	Asia, Africa, Europe	Glabridin, glabrene, isoliquiritigenin	Inhibits tyrosinase activity in a noncompetitive manner.[45,47]

Humulus japonicus	China, Japan, Korea, Taiwan and the Russian Far East	cis-N-coumaroyl tyramine, N-coumaroyl tyramine, Trans-N-coumaroyl and tyramine derivatives	Anti-melanogenic activity by inhibiting tyrosinase. [49,50]
Kojic acid and β-arbutin	N/A	Synthetic compounds	Inhibit tyrosinase activity and reduce melanin synthesis, reduce melanin content and improve cell viability.[75,76,76,78]
Koji Bean Seeds	Japan	7,3',4'-THIF, 7,8,4'-THIF	Inhibition of melanin production via MC1R interaction, Inhibition of monophenolase and bisphenolase tyrosinase activity. [54,55]
Lippia origanoides, (Aerial parts) Essential Oil	Southern north America	1,8-cineole, α-terpineol, thymol, β-caryophyllene, α-phellandrene, β-phellandrene, (E)-nerolidol	Inhibits tyrosinase activity and exhibits antioxidant capacity [74]
Methyl gallate	N/A	Polyphenolic compound	Inhibits activity of tyrosinase, and downregulates associated proteins of melanin synthesis, skin-whitening cosmetics [69,70,71,96].
Morus alba L.Twigs of Morus alba L.	China and India	Morusone Steppogenin	Tyrosinase inhibition with an IC_{50} value of 290.00 ± 7.90 Inhibits tyrosinase activity.[38,39]
Morus alba Linn. Twig extract	Middle east and southeast Asia	Steppogenin, oxyresveratrol, moracenin D, sanggenon T, kuwanon O, morusone	Inhibition of enzyme tyrosinase, potential for melanin inhibition, Anti browning agents [39]
Morus australis Root extract	China, Korea, Taiwan	Sanggenon-type sanggenon M, isoprenyl flavanone, Nigrasin K, sanggenon C, chalcomoracin, sanggenon O, kuwanon J, sorocein H	Inhibits tyrosinase activity, anti-browning and skin whitening [28,29]
Morus lhou	Central China	Mormin, Cyclomorusin, Morusin, Kuwanon C, Norartocarpetin, artocarpin, cycloartocarpin, and more	Inhibits tyrosinase enzymatic activity and time-dependent action against the oxidation of L-tyrosine. [66,67]
Paeonia lactiflora Pall. (root) (Aerial parts) Essential Oil	Central and eastern Asia	Gallic acid derivatives	Tyrosinase activity inhibition through chelation of copper, Promotes skin barrier

			function and exhibits antioxidant capacity. [72,73]
Phellinus linteus	Japan, China and Korea	Protocatechualdehyde, 5-hydroxymethyl-2-furaldehyde (HMF)	Remarkable tyrosinase inhibition. L-tyrosine oxidation inhibition. [57,58]
Rhus succedanea Lacquer tree sap	Asia	Alkyl hydroquinone 10'(Z)-heptadecenylhydroquinone	Inhibits tyrosinase activity. [34,35]
Scutellaria baicalensis	East Asia	Baicalein	Indirect inhibition of tyrosinase through phosphorylation of ERK and MITF, direct inhibition of tyrosinase, Anti-inflammatory activity [32,33]
Thymus quinquecostatus	China, Japan &Russia	Thymol	Inhibits tyrosinase activity and exhibits potential whitening activity.[66,67]
Vigna radiata L. Mung bean	Asia	Vitexin, isovitexin	Tyrosinase enzyme inhibitors with IC_{50} value of 6.3 and 5.6 µ mL^{-1}, respectively [41,42,43]

Fig .2 : Provided figure presents a summary of several plant species potential as sources of natural compounds with tyrosinase inhibitory activity.36,53,60,63,49,75,66,41

CONCLUSION:

In summary, the skin is a complex and important organ made up of layers that work together to provide protection and vitality. Tyrosinase is an important enzyme involved in the synthesis of melanin, which plays an important role in determining the color of the skin. Inhibition of tyrosinase activity is the main strategy for skin lightening, aimed at reducing melanin production and alleviating hyperpigmentation. Tyrosinase inhibitors interfere with several steps in the melanin synthesis pathway, such as the conversion of tyrosine to melanin precursors, ultimately leading to fair skin. There are many treatments for skin hyperpigmentation and whitening, from medical procedures such as chemical peels and LED treatments. These treatments offer different ways to target and control hyperpigmentation, but each has its own benefits and side effects. In seeking balance, even tone in the face, it is important to understand the difference between various treatments available and their effects. Natural plant extracts are noted for their ability to be effective and safe against other lightning agents. The extracts were found to have a significant effect on melanin production without damaging melanocytes. Various plants and their extracts demonstrate the potential of natural bioactive ingredients in skin whitening and hyperpigmentation treatment. These ingredients exhibit a range of effects on tyrosinase from competitive inhibition to direct inhibition, thus showing promise for depigmentation and skin lightening formulations. The interaction of natural compounds with tyrosinase and the melanogenesis pathway provides an important basis for their application in skin care and cosmetics. Compounds such as mormin, cyclomorusin, kuwanon C, and morusin from Morus lhou, as well as dihydromorin and norartocarpetin from Artocarpus heterophyllus, exhibit inhibitory behaviors against tyrosinase and melanin oxidation. Methyl gallate, gallic acid, and polyphenolic compounds further demonstrate their potential in downregulating melanin synthesis-associated proteins. Plant extracts like those from Paeonia lactiflora Pall. and Lippia origanoides contain gallo tannins and essential oil components that inhibit tyrosinase activity while promoting skin barrier function. Kojic acid, β-arbutin, and synthetic compounds are also recognized for their inhibitory roles in melanin synthesis. Furthermore, Andrographis paniculata, Thymus quinquecostatus, and Salviae Miltiorrhizae offer additional options with potential anti-melanogenic and skin whitening properties. Additionally, the utilization of natural extracts from Danshen-Honghua herbal pairs, Morus alba Linn., Apios americana, Glycyrrhiza glabra, Cudrania cochinchinensis, and more, presents a diverse landscape of potential skincare ingredients. These ingredients exhibit a range of effects on tyrosinase from competitive inhibition to direct inhibition, thus showing promise for depigmentation and skin lightening formulations. A comprehensive review of these natural bioactive ingredients highlights the potential of plant-based ingredients in developing better, more effective skincare products. With further research, these discoveries pave the way for harnessing the natural resources to create new skin treatments that will meet the needs of a variety of skin types and concerns. Therefore, bioactive components of various species of Herbs and plant extracts have the capability of being used in skincare and cosmetics.

ABBREVIATION

cAMP - (PKA)	Cyclic Adenosine Monophosphate -Dependent Protein Kinase A
CD	Circular Dichroism
DHI	Dihydroxy indole
DHICA	Dihydroxyindole-2-carboxylic acid

DQ	Dopaquinone
ESI-MS	Electrospray Ionization Mass Spectrometry
HEM	Human Epidermal Melanocytes
HPLC	High-Performance Liquid Chromatography
HQ	Hydroquinone
HSYA	Hydroxysafflor Yellow A
IC	Inhibitory Concentration
LED	Light Emitting Diode
MC1R MEK/ERK	Melanocortin 1 Receptor Mitogen-Activated Protein Kinase/ Extracellular Signal-Regulated Kinase
MSH MITF MTYR	Melanocortin 1 Receptor Mitogen-Activated Protein Kinase/ Extracellular Signal-Regulated Kinase
MSH	Melanocyte-Stimulating Hormone-Induced
MITF	Microphthalmia-associated transcription factor
MTYR	Melanocyte-Stimulating Hormone-Induced Microphthalmia-associated transcription factor Mushroom tyrosinase
NMR	Nuclear Magnetic Resonance
p38 MAPK PI3K/PKB	p38 Mitogen-Activated Protein Kinase Phosphoinositide 3-Kinase/ Protein Kinase B
PKB	Protein Kinase B
THIF	Trihydroxy isoflavone
TYR	Tyrosine
UV	Ultraviolet

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HOW TO CITE: Sirisha N. V. L. Mulukuri, Anushree Munchinamane P., Satheesh Madhav N. V., Pankaj Kumar, Advances In Skin Lightening Agents: Mechanisms, Efficacy, And Safety Considerations, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 6, 998-1019. https://doi.org/10.5281/zenodo.12105303